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Bridging the gap between Transcriptome and Metabolome by using Genome-scale Metabolic Models

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Motivation

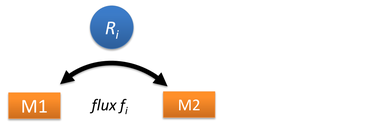
The direct *in vivo* investigation of metabolism is complicated by the fact that it is not yet possible to quantitatively measure all metabolite levels within the cell. Thus, there is a need for development of methods that enable to predict whether a particular metabolite is being accumulated or depleted following a genetic/environmental perturbation. Towards this goal, a computational method is presented for integrating transcriptome data and genome-scale metabolic models for predicting accumulation or depletion of intracellular metabolites.

Methods

Reaction Directionality Analysis (RDA)

Subject to

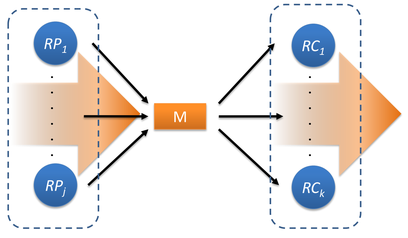
Fixed fermentation physiological parameters, network stoichiometry

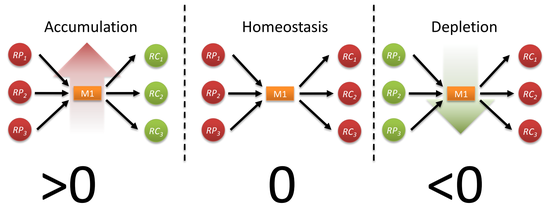


foreach R_i *maximize && minimize* f_i

Linear programming (LP) problem is solved for maximizing and minimizing each flux f_i , thus resulting in a system flexibility under constraint of fixed substrates uptake and biomass production. In other words, the method aims at checking each reaction`s behavior – whether it can go either in both directions but still maintaining main flux towards cellular objective production, or only in one direction.

Metabolite Scoring System





$$S = \frac{\sum_{i=1}^{j} RP_i}{j} + \frac{\sum_{i=1}^{k} RC_i}{k}$$

$$RP_i = FP_i \times PP_i$$

$$FP_i = \begin{cases} \mathbf{1} \text{ if log(fold change) of gene controlling } RP_i > 0 \\ \mathbf{-1} \text{ if log(fold change) of gene controlling } RP_i < 0 \end{cases}$$

$$PP_i = \begin{cases} \mathbf{1} \text{ if } p\text{-value of gene controlling } RP_i \leq 0.05 \\ \mathbf{0.5} \text{ if p-value of gene controlling } RP_i > 0.05 \end{cases}$$

$$RC_i = FC_i \times PC_i$$

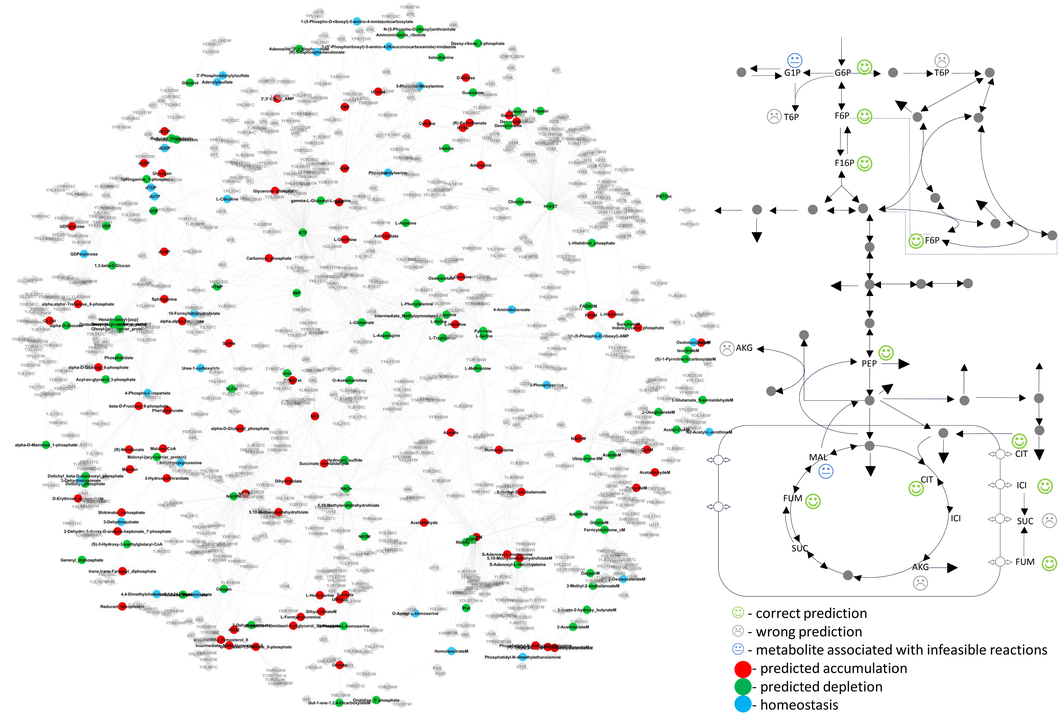
$$FC_i = \begin{cases} \mathbf{-1} \text{ if log(fold change) of gene controlling } RC_i > 0 \\ \mathbf{1} \text{ if log(fold change) of gene controlling } RC_i < 0 \end{cases}$$

$$PC_i = \begin{cases} \mathbf{1} \text{ if } p\text{-value of gene controlling } RC_i \leq 0.05 \\ \mathbf{0.5} \text{ if } p\text{-value of gene controlling } RC_i > 0.05 \end{cases}$$

Conclusions

The proposed method is able to qualitatively predict intracellular metabolite pool change between two different physiological conditions. Accumulation/depletion of metabolites were successfully predicted in 73% of the cases. Methodology can be used, for example, as a guiding tool for making targeted metabolome analysis and biomarker development. An interesting application will be in human diseases research, where transcriptomic phenotype is more readily measurable than metabolome.

Results



- Out of 1433 metabolic reactions, 507 are predicted by RDA to have *forward* direction, *40 backward*, 230 (out of 405) *reversible* and 656 *infeasible*.
- Changes in 220 metabolite pools are predicted, out of them - 112 are being accumulated , 107 depleted and 49 are at homeostasis state
- Experimental measurements of 11 metabolites levels [1] were used as a proof of concept, the direction of change of 8 metabolites were correctly predicted.

References:

1. Kresnowati MT, van Winden WA, Almering MJ, ten Pierick A, Ras C, et al. (2006) When transcriptome meets metabolome: fast cellular responses of yeast to sudden relief of glucose limitation. Mol Syst Biol 2: 49.